REMARKS/ARGUMENTS

It is requested that the IDS filed June 25, 2003 be considered in this application.

Claim 1 is amended to include a particular feature of the chemical structure of the antibacterial substance, namely that it is chemically bonded to the reduced end sugar of a sulfated polysaccharide or of the oligosaccharide. This is supported by the description on page 4, line 28 to page 5, line 15, particularly, on page 5, lines 3-4.

Claims 4 and 5 corrects the typographical error noted by the Examiner.

The present invention as defined in claim 1 provides a novel antibacterial agent which enables its compound to be stable on the gastric wall and has high antibacterial effect and specific affinity for *Helicobactor pylori*, since the antibacterial substance is chemically bonded to the reduced end sugar of the sulfated polysaccharide or of the oligosaccharide, such as fucoidan, carrageenan, etc., which has high affinity for *Helicobactor pylori* to inhibit its fixation on gastric wall.

The Examiner rejects claims 1, 4 and 5 as being anticipated by Walton (USP 4,489,065). Walton discloses a number of

conjugates comprising an antibacterial substance covalently bonded to chondroitin or chondroitin sulfate to form a prodrug which shows a controlled release behavior in vitro. As can be clearly understood from the description on column 3, lines 37-46 of Walton, this prodrug is a compound in which an antibacterial substance is bonded to a carboxy group of the structural saccharide of a chondroitin sulfate. This means that the chemical structure of the Walton's prodrug is clearly different from that of the antibacterial agent according to the present invention in which an antibacterial substance is chemically bonded to the reduced end sugar (1-position at the reduced end) of the sulfated polysaccharide or of the oligosaccharide.

Therefore, the present invention as defined by claim 1 is not disclosed by Walton.

The Examiner rejects claim 3 as being unpatentable over Walton et al (USP 4,489,065) as applied to claims 1, 4 and 5, and further in view of Dadey (WO 97/37680).

Walton teaches a prodrug having a chemical structure which differs from that of the present invention as discussed above.

Due to the different position of the chemical bond, Walton's prodrug shows a controlled release behavior, and therefore, the

prodrug is unstable and believed not to have antibacterial activity which is sufficient to use as a medicine for the eradication of *Helicobactor pylori*.

Contrary to the prodrug of Walton, it is not acceptable for the antibacterial agent of the present invention to have less medicinal stability, since the antibacterial substance is to be delivered to a portion of gastric wall (on which *Helicobactor pylori* exists) by means of the sulfated polysaccharide which has high affinity for *Helicobactor pylori*, thereby achieving high antibacterial effect and specific affinity for *Helicobactor pylori* to inhibit its fixation on gastric wall.

Walton gives no information nor motivation to provide the medicinal stability of an anti-ulcer agent on gastric wall, since Walton does not teach nor suggest an antibacterial compound containing a polysaccharide which has high affinity for *Helicobactor pylori* and an antibacterial substance which is chemically bonded to the reduced end sugar of the polysaccharide to produce medicinal stability and high antibacterial effect of the compound on gastric wall.

As to Dadey, the Examiner's opinion is that carrageenan is a functional equivalent of chondroitin sulfate in the preparation

of poly/origo-saccharide-drug conjugates. Dadey, however, discloses a macromolecular drug composition suitable for long term administration, which composition contains a drug such as insulin and a polymer. The composition clearly differs from the present invention in chemical structure and purpose or object thereof. On page 14, lines 15-30, Dadey suggests the use of heparin, chondroitin sulfate, carrageenan and mixture thereof, as useful naturally occurring polymers. However, this suggestion merely relates to a choice of polymer in conjugation with insulin (see, page 14, lines 6-14). Also, Dadey does not disclose an antibacterial agent having high antibacterial effect and specific affinity for *Helicobactor pylori* on gastric wall.

Further, the teachings of Dadey differ from that of Walton in purpose or object of the invention and do not relate to an antibacterial agent. Therefore, Dadey does not give any motivation to substitute carrageenan for chondroitin sulfate of Walton. That is, since Dadey only teaches a macromolecular drug complex which is formed by a protein such as insulin and a polymer such as sulfated polysaccharide for the purpose of long term stable administration, no one would have been motivated by Dadey to substitute carrageenan for chondroitin sulfate which is

to be bonded to an antibacterial substance to form a prodrug of Walton.

The present invention provides an antibacterial compound containing a - polysaccharide which has high affinity for *Helicobactor pylori* and an antibacterial substance which is chemically bonded to the reduced end sugar of the polysaccharide to produce the medicinal stability and high antibacterial effect of the compound on gastric wall, and is believed to be patentable over Walton in view of Dadey.

The Examiner rejects claims 1-3 and 7 as being unpatentable over Domb et al (USP 6,011,008) in view of Josephson et al (USP 5,336,506). Domb discloses a conjugate composition of oxidized arabinogalactan and mitomycin. However, the oxidized arabinogalactan is not sulfated polysaccharides, and as shown in Fig. 1 of Domb, the conjugate composition is an unstable chemical compound in which mitomycin is bonded to the hydroxyl group of the structural sugar of the oxidized arabinogalactan, whereas the antibacterial agent according to the present invention has a chemical structure in which an antibacterial substance is chemically bonded to the reduced end sugar of the sulfated polysaccharide or of the oligosaccharide to produce the medicinal

stability and high antibacterial effect as well as specific affinity for *Helicobactor pylori* on gastric wall. Therefor, the conjugate composition of Domb clearly differs from the present invention in chemical structure. Further, Domb merely teaches the preparation of water-soluble oxidation sensitive substances which are suitable for parenteral administration. Domb does not disclose nor suggest how to increase the medicinal stability and antibacterial effect of the drug as well as specific affinity for *Helicobactor pylori* on gastric wall.

Josephson discloses that arabinogalactan mannan and fucoidan may be used to deliver therapeutic agents directly to hepatocytes and macrophages respectively (col. 4, lines 24-28). However, Josephson does not disclose nor suggest that these RME-type polysaccharides have high affinity for *Helicobactor pylori* on gastric wall. Particularly, Josephson merely teaches a method for targeting a therapeutic agent to a specific population of cell (such as hepatocytes) by means of receptor mediated endocytosis (RME), and this method differ form the present invention in which an antibacterial substance is bonded to the reduced end sugar of the sulfated polysaccharide to enhance the specific affinity for *Helicobactor pylori* on gastric wall while

maintaining the medicinal stability and high antibacterial effect of the drug. Further, in the teachings of Josephson, the objective agent is attached to a polysaccharide with acid amide bond or ester bond to facilitate the agent to be targeted to a specific population of cell, such as hepatocytes. Contrary to this teachings, the antibacterial agent according to the present invention has a chemical structure in which an antibacterial substance is chemically bonded to the reduced end sugar of the sulfated polysaccharide to facilitate the antibacterial substance to be directed to a specific bacteria, *Helicobactor pylori*, on gastric wall, with specific affinity therefor. Therefor, the teachings of Josephson clearly differs from the present invention.

The Examiner rejects claims 1-3 and 7 as being unpatentable over Domb et al CUSP 6,011,008) in view of Josephson et al (USP 5,336,506) in further view of Dadey (WO 97/37680).

As set forth above, Domb discloses a conjugate composition of oxidized arabinogalactan and mitomycin. The oxidized arabinogalactan is not sulfated polysaccharides, and the conjugate composition is an unstable chemical compound in which mitomycin is bonded to the hydroxyl group of the structural sugar

of the oxidized arabinogalactan. Domb merely teaches the preparation of water-soluble oxidation sensitive substances which are suitable for parenteral administration. Domb does not disclose nor suggest how to increase the medicinal stability and antibacterial effect of the drug as well as specific affinity for *Helicobactor pylori* on gastric wall.

Josephson discloses that arabinogalactan mannan and fucoidan may be used to deliver therapeutic agents directly to hepatocytes and macrophages respectively (col. 4, lines 24-28). However, Josephson does not disclose nor suggest that these RME-type polysaccharides have high affinity for *Helicobactor pylori* on gastric wall. Particularly, Josephson merely teaches a method for targeting a therapeutic agent to a specific population of cell (such as hepatocytes) by means of receptor mediated endocytosis (RME), and this method differ form the present invention in which an antibacterial substance is bonded to the reduced end sugar of the sulfated polysaccharide to enhance the specific affinity for *Helicobactor pylori* on gastric wall while maintaining the medicinal stability and high antibacterial effect of the drug. Further, in the teachings of Josephson, the objective agent is attached to a polysaccharide with acid amide

bond or ester bond to facilitate the agent to be targeted to a specific population of cell, such as hepatocytes. Contrary to this teachings, the antibacterial agent according to the present invention has a chemical structure in which an antibacterial substance is chemically bonded to the reduced end sugar of the sulfated polysaccharide to facilitate the antibacterial substance to be directed to a specific bacteria, *Helicobactor pylori*, on gastric wall, with specific affinity therefor.

Dadey discloses a macromolecular drug composition suitable for long term administration, which composition contains a drug such as insulin and a polymer. The composition clearly differs from the present invention in chemical structure and purpose or object thereof. On page 14, lines 15-30, Dadey suggests the use of heparin, chondroitin sulfate, carrageenan and mixture thereof, as useful naturally-occurring polymers. However, this suggestion merely relates to a choice of polymer in conjugation with insulin (see, page 14, lines 6-14). Also, Dadey does not disclose an antibacterial agent having high antibacterial effect and specific affinity for *Helicobactor pylori* on gastric wall.

Further, the teachings of Dadey differ from those of Domb and/or Josephson in purpose or object of the invention and do not

relate to an antibacterial agent. Therefore, Dadey does not give any motivation to substitute carrageenan for arabinogalactan of Domb/Josephson. That is, since Dadey only teaches a macromolecular drug complex which is formed by a protain such as insulin and a polymer such as sulfated polysaccharide for the purpose of long term stable administration, no one would have been motivated by Dadey to substitute carrageenan for arabinogalactan which is to be bonded to mitomycin in the preparation of water-soluble oxidation sensitive substances of Domb or for arabinogalactan which is to be bonded to a therapeutic agent in the method for targeting a therapeutic agent to a specific population of cell, such as hepatocytes which is not a bacteria, by means of RME as shown by Josephson.

The present invention provides an antibacterial compound containing a polysaccharide which has high affinity for *Helicobactor pylori* and an antibacterial substance which is chemically bonded to the reduced end sugar of the polysaccharide to produce the medicinal stability and high antibacterial effect of the compound on gastric wall, and is believed to be patentable over Domb et al in view of Josephson et al in further view of Dadey.

In view of the above, it is submitted that the present invention is not shown or suggested by the cited art. Withdrawal of the rejections and allowance of the application are respectfully requested.

Respectfully submitted,

Frishauf, Holtz, Goodman
& Chick, P.C.
767 Third Ave., 25th Floor
New York, NY 10017-2023
Tel. No. (212) 319-4900
Fax No.: (212) 319-5101
MJC/ld

MARSHALL J. CHICK
Reg. No. 26,853